REMARKS:

Claims 1 to 11 are pending in the application. Claims 1 to 3 and 6 to 11 have been withdrawn from consideration as drawn to a non-elected invention. Claims 4 and 5 are currently under consideration.

Applicants have amended claim 4 to incorporate the definition of R from withdrawn claim 1 and to add a third step of identifying which test substance inhibits acylated homoserine lactone. That amendment finds support in the specification, at least at page 17, lines 9 to 22, which discloses that:

> when animal cells are cultured with a test substance in the presence of acylated homoserine lactone, the Akt-activity-inhibiting effect of acylated homoserine lactone, which is observed in the case of culture without the test substance, would not be observed or would be observed to decrease, and the test substance can be identified to be a substance inhibiting acylated homoserine lactone.

Applicants have amended claim 5 to be consistent with the amendments to claim 4. Applicants have also added new claim 12, support for which can be found in the specification, at least at page 19, lines 6 to 11, which discloses that:

> when animal cells are cultured with a test substance in the presence of acylated homoserine lactone, a caspase-activating effect of acylated homoserine lactone, which is observed in the case of cultures without any test substance, would not be observed or would be observed to decrease, and the test substance can be identified as a substance inhibiting acylated homoserine lactone.

Thus, the amendments are fully supported and add no new matter.

Applicants thank the Examiner for withdrawing the Office Action of January 29, 2007, in favor of the March 27, 2007, Office Action.

Priority

Applicants thank the Examiner for acknowledging their claim for foreign priority based on Japanese patent application nos. JP 2003-021047 and JP 2003-021053.

The Examiner also stated that "applicant has not filed a certified copy of the JP 2003-[0]21053 application as required by 35 U.S.C. 119(b)." Office Action mailed March 27, 2007 ("Office Action"), at page 3. Applicants note that they provided certified copies of both priority applications when they filed this application on January 28, 2004, as indicated on the transmittal sheet and acknowledged on the postcard (copies attached).

Information Disclosure Statement

Applicants thank the Examiner for acknowledging the Information Disclosure Statements filed on July 20, 2004, and on August 29, 2004. Office Action, at page 3.

Drawings

Although the Examiner objected to Figure 14 under 37 C.F.R. 1.83(a) "because [it] fail[s] to show the result of determining apoptosis in cells in the presence of acylated homoserine lactone by chromatic condensation using Hoechst 3341 staining as described in the specification on page 9," Office Action, at pages 3 to 4, that issue appears to have been resolved. Specifically, the undersigned telephoned the Examiner on March 6, 2007, to clarify whether the objection was based on the scanned black and white version of Figure 14 in the Image File Wrapper on Private PAIR, or on the color photographs filed with the application. In a voice mail message left for the undersigned on March 7, 2007, the Examiner indicated that the objection was based on the scanned black and white version of Figure 14 in the Image File Wrapper. The Examiner also acknowledged receipt of (1) a Petition to Accept Color Photographs under 37 C.F.R. §

1.84(b)(2); (2) three sets of color photographs of Figure 14; and (3) a Preliminary Amendment amending the specification to include the required statement regarding inclusion of color photographs in the application, submitted with the application on January 28, 2004.

Applicants thank the Examiner for acknowledging that Applicants have complied with the requirements for submission of color photographs, and therefore respectfully ask the Examiner to reconsider and withdraw this objection.

Claim Rejections under 35 U.S.C. § 102

The Examiner rejected claim 4 under 35 U.S.C. § 102(b) as allegedly anticipated by Smith et al. (2001) *J. Immunol.* 167:366-374 ("Smith"), as evidenced by Zimmerman et al. (1999) *Science* 286:1741-1744 ("Zimmerman"). Office Action, at page 5.

The Examiner alleged that Smith teaches:

> a method of determining the [e]ffects of 3-O-C12-HSL (N-3-oxododecanoyl homoserine lactone) on MAP kinases, comprising contacting 16HBE cells with a test substance in the presence of 3-O-C12-HSL and determining the activation of ERK (page 371, 1st column, 1st full paragraph to 2nd column). Specifically, the reference teaches that the test compound completely inhibited the induction of ERK by 3-O-C12-HSL (page 372, Fig. 8).

Id. The Examiner does recognize that Smith does not provide two of the elements of the claims but relies on the doctrine of inherent anticipation to provide the first element and on the supposition that the preamble does not limit the invention because it does not "result in a manipulative difference" between the claimed method and the disclosure of the prior art to ignore the lack of the second element.

First, regarding the doctrine of inherent anticipation, the Examiner conceded that Smith "do[es] not specifically teach that Erk is involved in the survival signaling pathway in which Akt is involved," but contends that Zimmerman showed that the "the Akt signaling pathway is

inherently associated with Erk." After asserting that "the claimed limitation does not appear to result in a manipulative difference in the method steps when compared to the prior art[']s disclosure," the Examiner looked to Zimmerman for the alleged showing that phosphorylation of Raf by Akt inhibited activation of the Raf-MEK-ERK signaling pathway.

Applicants respectfully traverse. As is well established, the doctrine of inherency requires the Examiner to provide "a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." MPEP § 2112 at page 2100-48 (quoting *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original)). Thus, the combination of references would have to show that inhibition of ERK necessarily correlates to inhibition of the Akt signaling pathway.

In fact, Zimmerman teaches the opposite. As set forth in the Abstract, Zimmerman acknowledges that Akt is "a member of a different signaling pathway" than the Raf-MEK-ERK signaling pathway. *See also* Zimmerman, at pages 1741-42 (noting that the Akt pathway is "another" pathway). At most, Zimmerman shows that there can be "cross talk" between the two different signaling pathways. *See* Abstract and page 1743. But the existence of cross talk does not establish that the inhibition of ERK or any other component of the Raf-MEK-ERK signaling pathway in Smith necessarily inhibits Akt activity. Moreover, Zimmerman provides no suggestion that inhibition of ERK leads to inhibition of Akt. Instead, Zimmerman shows only that, in some cell systems, Akt can inhibit activation of the Raf-MEK-ERK pathway. Zimmerman, at page 1743, last paragraph. Accordingly, Zimmerman does not demonstrate that the inhibition of ERK by the test compound necessarily shows "inhibition of Akt activity." For at least this reason, Smith does not anticipate the claimed invention.

Second, the Examiner conceded that Smith does not "explicit[ly] teach a method of screening for a substance inhibiting acylated homoserine lactone," but ignores the absence of this limitation by asserting that "the claimed preamble does not appear to result in a manipulative difference between the active steps claimed and those disclosed by the prior art, i.e., culturing animal cells with a test substance in the presence of acylated homoserine lactone and detecting inhibition of the survi[v]al signaling pathway in which Akt is involved in the cells." *Id.*

Applicants again respectfully traverse. While it is correct that preambles do not always establish claim limitations, the MPEP makes clear that:

> Any terminology in the preamble that limits the structure of the claimed invention must be treated as a claim limitation. *See, e.g., Corning Glass Works v. Sumitomo Elec. U.S.A., Inc.*, 868 F.2d 1251, 1257, 9 USPQ2d 1962, 1966 (Fed. Cir. 1989) (The determination of whether preamble recitations are structural limitations can be resolved only on review of the entirety of the application "to gain an understanding of what the inventors actually invented and intended to encompass by the claim.") . . . .

MPEP § 2111.02(I), at page 2100-42.

Here, the preamble recites "a method of screening for a substance that inhibits acylated homoserine lactone" and the body of the claim recites "culturing animal cells with a test substance in the presence of acylated homoserine lactone," "detecting inhibition of Akt activity," and "identifying the substance as one that inhibits acylated homoserine lactone." Thus, the elements of screening, culturing, detecting inhibition of Akt activity, and identifying the substance as one that inhibits acylated homoserine lactone are claim limitations and must be present in the anticipatory reference. As the Examiner has acknowledged, the screening element is not present in the cited documents. Moreover, the step of "detecting inhibition of Akt activity" results in a manipulative difference between the claimed method and the cited documents, which

disclose "determining the activation of ERK." As discussed above, neither Smith nor Zimmerman shows that determining the activation of ERK by the test compound necessarily correlates with "inhibition of Akt activity." Thus, for at least these reasons, Smith does not anticipate the claimed invention.

Accordingly, Applicants respectfully assert that Smith, as evidenced by Zimmerman, does not teach each and every element of claim 4, and therefore cannot anticipate the claimed invention. Applicants therefore request reconsideration and withdrawal of the rejection of claim 4 under 35 U.S.C. § 102(b).

Claim Rejections under 35 U.S.C. § 103

The Examiner rejected claim 5 under 35 U.S.C. § 103(a) as allegedly unpatentable over Smith, as evidenced by Zimmerman, in view of Koo et al. (US Patent Publication No. 2002-0054869) ("Koo"). Office Action, at page 6.

Specifically, the Examiner again alleged that Smith, as evidenced by Zimmerman teach "a method of determining the [e]ffects of 3-O-C12-HSL (N-3-oxododecanoyl homoserine lactone) on the MAP kinase signaling pathway, comprising contacting 16HBE cells with a test substance in the presence of 3-O-C12-HSL and determining the activation of ERK, wherein the test compound [PD98059] completely inhibited the induction of ERK by 3-O-C12-HSL." *Id.* Claim 5 further recites that "inhibition" is "detected by detecting apoptosis," and the Examiner conceded that Smith "do[es] not explicitly teach that the inhibition of ERK is determined by detecting apoptosis." To fill this gap, the Examiner relied on Koo for allegedly teaching that "inhibition of the MAP kinase signaling pathway specifically triggers an apoptotic response in human cells . . . [and] that inhibitors of the MAP kinase signaling pathway such as PD9805[9]

are useful for inhibiting the growth of a tumor in a mammal, wherein the inhibitor induces a cytotoxic response leading to apoptosis of cells in said mammal." *Id.*

The Examiner therefore concluded it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made "to combine the teachings of the references so as to determine the affects of 3-O-C12-HSL (N-3-oxododecanoyl homoserine lactone) on the MAP kinase signaling pathway in the presence of a test compound as taught by Smith et al. by detecting apoptosis of the cell in view of Koo et al. with a reasonable expectation of success." *Id.*, at page 6. The Examiner further asserted that a skilled artisan would have been motivated to combine the references "because [K]oo et al. teach that is well known in the art that the inhibition of the MAP kinase signaling pathway triggers an apoptotic response in human cells; and further that inhibitors of the MAP kinase signaling pathway are well known to induce apoptosis." *Id.*

Applicants respectfully traverse. Claim 5 depends from claim 4, and therefore includes all of the limitations of that claim. MPEP § 608.01(n) (citing 37 C.F.R. § 1.75(c)). As discussed above, the method of claim 4 requires a step of "detecting inhibition of Akt activity." Neither Smith, Zimmerman, nor Koo teach that activation of the Raf-MEK-ERK MAP kinase signaling pathway according to Smith inhibits Akt activity. On the contrary, the Examiner acknowledged that Smith "do[es] not specifically teach that Erk is involved in the survival signaling pathway in which Akt is involved in." Office Action, at page 5. Furthermore, as also discussed above, Zimmerman does not teach or suggest that ERK or any other component of the Raf-MEK-ERK MAP kinase signaling pathway inhibits Akt activity.

Moreover, while the doctrine of inherency may apply to rejections for lack of novelty, it cannot apply in the context of obviousness because, as set forth by the Federal Circuit in *In re Rijckaert,* 28 USPQ2d 1955 (Fed. Cir. 1993):

> "That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown." *In re Spormann*, 363 F.2d 444, 448, 150 USPQ 449, 452 (CCPA 1966). Such a retrospective view of inherency is not a substitute for some teaching or suggestion supporting an obviousness rejection. *See In re Newell*, 891 F.2d 899, 901, 13 USPQ2d 1248, 1250 (Fed. Cir. 1989).

Finally, Koo teaches that inhibition of the Raf-MEK-ERK MAP kinase signaling pathway selectively induced apoptosis in melanoma cells, and makes absolutely no mention of the Akt signaling pathway, or of acylated homoserine lactone. *See* Koo, at paragraphs [0012-0013].

Also as noted above, the present invention relates to a "method of screening for a substance that inhibits acylated homoserine lactone," and none of the references, individually or in combination, provide this element.

Accordingly, Applicants respectfully assert that the cited combination of Smith, as evidenced by Zimmerman, in view of Koo, does not render the claimed invention obvious. Applicants therefore request reconsideration and withdrawal of the rejection of claim 5 under 35 U.S.C. § 103(a).

The Examiner also rejected claims 4 and 5 under 35 U.S.C. § 103(a) as allegedly unpatentable over Pearson et al. (U.S. Patent No. 5,591,872) ("Pearson") in view of Tateda et al. (2003) *Infection & Immunity* 71:5785-5793 ("Tateda"). Office Action, at page 6.

Specifically, the Examiner alleged that Pearson teaches

> a method of selecting inhibitors of the autoinducer molecule N-(3-oxododecanoyl)homoserine lactone, comprising contacting the autoinducer

> molecule with a suspected inhibitor, measuring the ability of the treated autoinducer molecule to stimulate the activity of a selected gene then determining whether the inhibitor represses or enhances the activity of the autoinducer molecule (column 5, lines 46-55).

Id. The Examiner conceded that Pearson "do[es] not explicitly teach that the method comprising culturing animal cells with the test agent and acylated homoserine lactone and detecting the inhibition of the survival signaling pathway which Akt is involved in, e.g., apoptosis." *Id.*

The Examiner relied on Tateda for its teaching "that the *Pseudomonas aeruginosa* autoinducer N-3-oxododecanoyl homoserine lactone accelerates apoptosis in critical cell populations, macrophages and neutrophils (page 5792, 1st column, 2nd paragraph). Therefore, the Examiner concluded it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made "to culture a test substance in the presence of N-3-oxododecanoyl homoserine lactone as taught by Pearson et al. in an animal cell such as a neutrophil and to identify an inhibitor of N-3 oxododecanoyl homoserine lactone by detecting apoptosis in view of the teachings of Tateda et al." *Id.*, at page 7.

For motivation, the Examiner relied on the alleged teaching in Tateda that N-3-oxododecanoyl homoserine lactone-induced apoptosis "plays a crucial role in the pathogenesis of *P. aeruginosa* infection." *Id.* Finally, for a reasonable expectation of success, the Examiner noted that "one would achieve an effective method of identifying a suitable inhibitor for the treatment of an immunocompromised host infected by P. aeruginosa, e.g., a person afflicted with cystic fibrosis." *Id.*

Applicants respectfully traverse. The Examiner noted that Applicants "cannot rely upon the foreign priority papers to overcome this rejection because a translation of said papers has not been made of record in accordance with 37 C.F.R. 1.55." Office Action, at page 7. Applicants

submit herewith English translations of Japanese Patent Application Nos. 2003-21047 and 2003-21053, both of which were filed on January 29, 2003. Because Tateda was not published until October 2003, several months after the priority documents were filed, it is not available as a reference under 35 U.S.C. § 103(a).

Furthermore, Pearson alone does not render the claimed method obvious, because it does not teach or suggest all the limitations of the claimed invention. The claimed method requires a step of "detecting inhibition of Akt activity." As the Examiner acknowledged, Pearson "do[es] not explicitly teach that the method comprising culturing animal cells with the test agent and acylated homoserine lactone and detecting the inhibition of the survival signaling pathway which Akt is involved in, e.g., apoptosis." *Id.* In fact, Pearson does not teach or suggest anything regarding the Akt signaling pathway in animal cells or apoptosis.[1] Thus, Tateda is not available as a reference under 35 U.S.C. § 103(a), and the Examiner has failed to establish that Pearson alone teaches or suggests all the limitations of claims 4 and 5.

Accordingly, Applicants respectfully assert that the cited combination of Pearson, in view of Tateda, does not render the claimed invention obvious. Applicants therefore request reconsideration and withdrawal of the rejection of claims 4 and 5 under 35 U.S.C. § 103(a).

Conclusion

In view of the foregoing remarks, Applicants respectfully request reconsideration and withdrawal of these rejections and timely allowance of the pending claims. Should the Examiner have remaining questions or concerns regarding this application, Applicants request that the

[1] Akt is a serine/threonine kinase which acts downstream of phosphatidylinositide 3-OH kinase ("PI3K"). Specification at page 12. The PI3K-Akt pathway is known as one of the survival signaling pathways. *Id.*

Examiner contact the undersigned at (650) 849-6617 to schedule an interview to discuss the application.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: June 27, 2007

By: _____
David C. Hoffman
Reg. No. 59,821

The Commissioner is hereby authorized to charge any additional filing fees due and any other fees due under 37 C.F.R. § 1.16 or §1.17 during the pendency of this application to our Deposit Account No. 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

By: _____
Ernest F. Chapman
Reg. No. 25,961

EFC/FPD/sci
Enclosures